

Rejections under 35 USC §102

Claims 1-3, 15-17, 19-20, 22, 29-31 and 33-34 were rejected under 35 USC §102(a, e) as anticipated by Norman, et al.. Applicant respectfully traverses this rejection as it pertains to Claims 22, 29-31 and 33-34; the remainder of the claims listed above have been cancelled.

Applicant respectfully submits that the compounds shown in Norman at columns 78-79 do not anticipate the presently claimed compounds. For example, the compound shown at the bottom of column 78, when viewed with the nitrogen of the pyrimidine ring at the bottom of the drawing, this being the "1" position in the formula, has an -OH group at the four position (corresponding to X in the claimed formula); an -OH group is not listed in the Markush group for X as recited in Claims 22 or 29. Moreover, when viewed as described above, the Norman compound has the nitrogen in the pyrrolo ring in the 5 position, while in the present claims this nitrogen is in the 7 position; and, the phenyl group in Norman is attached directly to the pyrrolo ring, while in the present compounds R₃ is attached via X₂ which is a 1-3 atom bridge. Similarly, the compound shown in column 79 has the phenyl groups attached directly to the pyrimidine and pyrrolo rings. Applicant respectfully submits that these compounds do not anticipate the claimed compounds and requests withdrawal of this basis of rejection.

Claims 1-3, 15-20 were rejected under 35 USC §102(b) as anticipated by Gangjee; Claims 1-2, 15-17, 19-20 were rejected under 35 USC §102(b) as anticipated by Traxler '457 or Traxler et al.; and Claims 1-2, 15-17, 19-20 were rejected under 35 USC §102(b) as anticipated by Missbach. All of these claims have been cancelled, thus obviating these rejections.

Rejections under 35 USC §112

Claims 15, 16, 19, 20, 29, 30, 33 and 34 are rejected under 35 USC §112, first paragraph, as not enabled for use of the term "an illness". Claims 15, 16, 19 and 20 are cancelled, obviating this aspect of the rejection as it pertains to these claims. As amended, Claim 29 now reads, "A method of inhibiting at least one enzyme selected from the group consisting of a receptor tyrosine kinase, dihydrofolate reductase and thymidylate synthase, for treatment of a disease condition in a patient, mediated by inhibition of any of these enzymes, by administering to a patient in need thereof an effective amount of a compound...". Applicant respectfully submits that the claims are enabled as to treatment of a disease condition which can be mediated by inhibition of these enzymes. The specification

describes at length the roles of these enzymes in many disease processes and thus the desirability of providing compounds which can inhibit these enzymes and interrupt or prevent the progression of many diseases.

Applicant has amended Claim 29 to refer to “a receptor tyrosine kinase”, to more clearly indicate that the term “receptor tyrosine kinase” is indeed more than one enzyme and refers to a family of enzymes as described in the specification at pages 1-2. Applicant respectfully submits that Claim 29 and the claims depending therefrom are enabled as to inhibition of RTKs generally. Applicant has provided data, in Table 4, establishing that compounds of the present invention can inhibit two, three or four of the receptor tyrosine kinases listed in the table. Applicant would like to call the Examiner’s attention to US Patent No. 6,462,060, a copy of which is enclosed, in which the United States Patent and Trademark Office determined that a similar showing of enzymatic activity and IC₅₀ values was sufficient to establish support for a genus embracing not only receptor tyrosine kinases, but all protein kinases. Applicant respectfully submits that, in view of the ‘060 patent, Applicant has sufficiently established that Claim 29 and dependent claims are enabled for use of the term “a receptor tyrosine kinase” and requests withdrawal of this basis of rejection.

Claims 17 (now cancelled) and 31 were rejected under 35 USC §112 as not enabled for use of the term “cancer”. As amended, Claim 31 now refers to disease conditions such as tumor growth, cell proliferation or angiogenesis. The inhibition of receptor tyrosine kinases, dihydrofolate reductase and thymidylate synthase is known in the art to prevent these conditions, and Applicant respectfully submits that Claim 31 is enabled for treatment of these conditions. One skilled in the art could easily screen the compounds of the present invention for in vivo inhibition of any of these enzymes and their ability to treat these disease conditions; such testing is routine and not undue as determined in *In re Wands*. In addition, this language was also deemed acceptable by the USPTO in the ‘060 patent.

Claims 1-11, 15-20, 22 and 29-34 were rejected under 35 USC §112, second paragraph, as indefinite for a variety of reasons. As it pertains to Claims 1-11 and 15-20 cancellation of these claims obviates this rejection. Applicant now addresses this basis of rejection as it pertains to the remaining pending claims and will refer to the numbered items in the office action.

1, 2, 3. Applicant has amended Claims 22 and 29 to more clearly indicate that X and X₂ are optionally present in the chemical formula (that is, at least one is present) and to clarify that divalent form of the substituent is used when X or X₂ is present. No new

matter is added; the claims as originally written specifically stated that at least one of X or X₂ is present.

4. Claim 3 has been cancelled, thus obviating the rejection as it pertains to this claim.

5, 6. Claims 22 and 29 have been amended to clarify the chemical terms, with the terms “alicyclic” replacing “cyclic aliphatic” and “heterocyclic” replacing “cyclic heteroaliphatic”.

7. The term “heteroaliphatic” has been deleted from the claims, thus obviating this basis of rejection. According to Hawley’s Condensed Chemical Dictionary, however, the term “aliphatic” does not appear to embrace atoms other than carbon.

8. Applicant respectfully submits that the term “prodrug” is not indefinite. One skilled in the art routinely identifies active metabolites and prodrugs of a compound; in fact, this information is required by the FDA for approval of a new drug. See also the ‘060 patent, column 11 lines 1-10, which provides additional references supporting this assertion; the claims of the ‘060 patent were determined not to be indefinite for use of this term, and no more guidance was provided in the ‘060 patent than in the present application.

9. Claim 34 has been amended and “including” replaced with “further comprising the step of”. Applicant respectfully submits Claim 34 is not indefinite. Claim 20 has been cancelled.

10. Applicant respectfully disagrees with the Examiner’s assertion that the material at page 29, lines 9-11 (“and any carbons or nitrogens of said alkyl group, alkenyl group, heteroalkyl group or heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons”) makes no sense and that such groups have been provided for. X and X₂ are from 1-3 atoms; the addition of this clause in the claim adds substituents that can be from 1-6 additional carbons or other atoms, resulting in a possible total of 9 atoms. Applicant respectfully submits that this language is not indefinite.

11. Claims 1 and 15 have been cancelled, thus obviating this basis of rejection.

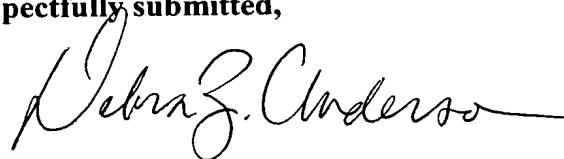
12. Claim 29 has been amended to refer to “a receptor tyrosine kinase”, as discussed above; this phrase is not indefinite.

Applicant respectfully submits that all §112, second paragraph issues have been addressed and requests withdrawal of this basis of rejection.

SUMMARY

As all outstanding issues have been addressed, Applicant respectfully submits that all pending claims, Claims 22 and 29-52 are now in condition for allowance; such action is respectfully requested at an early date.

Respectfully submitted,



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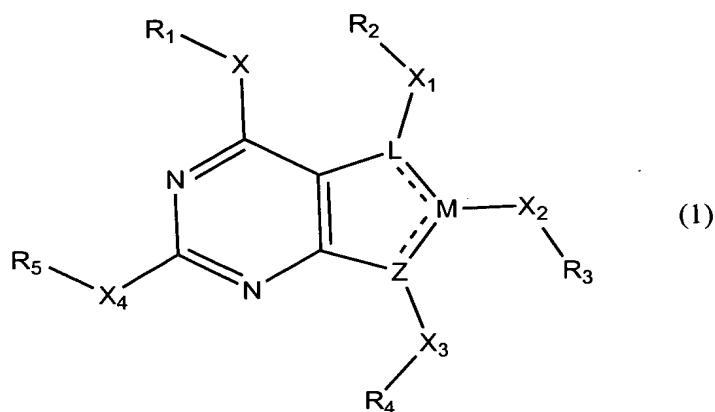
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APPENDIX

Additions are noted by underlining; deletions by strikethrough

In the specification:

Page 3, first paragraph under "SUMMARY OF THE INVENTION", which wraps through to page 5, line 15.

The present invention provides pyrimidine compounds, and pharmaceutically acceptable salts, solvates and prodrugs thereof, having the formula (1):



where X , X_1 , X_2 , X_3 and X_4 are from one to about three atoms, are the same or different and are independently selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, an heteroalkyl group and an heteroalkenyl group, and any carbons or nitrogens of said alkyl group, alkenyl group, heteroalkyl group or heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

Z is selected from the group consisting of C, CH, CH_2 , N, NH, S, O, $CH=CH$, $CH=N$ and $N=CH$;

L is selected from the group consisting of C, CH, CH_2 , N, NH, S, O, $CH=CH$, $CH=N$ and $N=CH$, but when Z is C, CH, $CH=CH$ or CH_2 then L is N, NH, S or O;

M is selected from the group consisting of carbon and CH;

the chemical bond between L and M is selected from the group consisting of a single bond and a double bond, and M is carbon when the bond is a double bond, and M is CH when the bond is a single bond;

the chemical bond between M and Z is selected from the group consisting of a single bond and a double bond, and M is carbon when the bond is a double bond, and M is CH when the bond is a single bond;

but when the bond between L and M is a double bond the bond between M and Z is a single bond;

at least one of R₂, R₃, R₄, or R₅ is present;

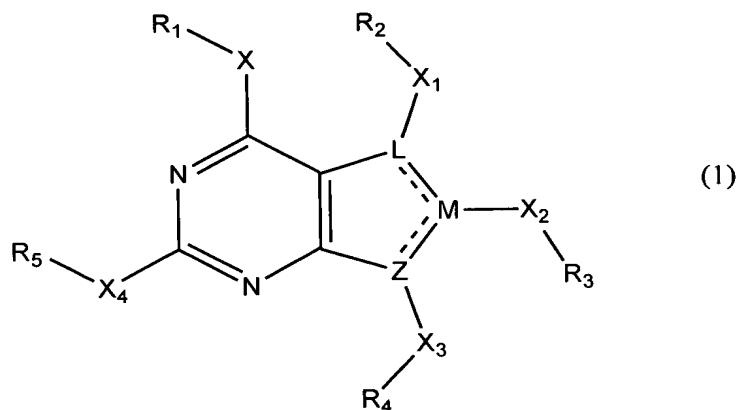
R₁, R₄ and R₅ are the same or different and are selected from the group consisting of hydrogen, a cyclic aliphatic an alicyclic group, a cyclic heteroaliphatic heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group and a substituted alkylheteroaryl group;

R₂ and R₄ are optional, are the same or different and are selected from the group consisting of hydrogen, a cyclic aliphatic an alicyclic group, a cyclic heteroaliphatic group, a cyclic aromatic group, a heterocyclic aromatic heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and *p*-acroyl-glutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or alkynl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

Page 7, first paragraph under "DETAILED DESCRIPTION OF THE INVENTION", which wraps through page 8, line 23.

The present invention is directed to compounds, and pharmaceutically acceptable salts, solvates, and prodrugs thereof, having formula (1):



where X , X_1 , X_2 , X_3 and X_4 are from one to about three atoms, are the same or different and are independently selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, a heteroalkyl group and a heteroalkenyl group,

and any carbons or nitrogens of said alkyl group, alkenyl group, heteroalkyl group or heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

Z is selected from the group consisting of C, CH, CH_2 , N, NH, S, O, $CH=CH$, $CH=N$ and $N=CH$;

L is selected from the group consisting of C, CH, CH_2 , N, NH, S, O, $CH=CH$, $CH=N$ and $N=CH$, but when Z is C, CH, $CH=CH$ or CH_2 then L is N, NH, S or O;

M is selected from the group consisting of carbon and CH;

the chemical bond between L and M is selected from the group consisting of a single bond and a double bond, and M is carbon when the bond is a double bond, and M is CH when the bond is a single bond;

the chemical bond between M and Z is selected from the group consisting of a single bond and a double bond, and M is carbon when the bond is a double bond, and M is CH when the bond is a single bond;

but when the bond between L and M is a double bond the bond between M and Z is a single bond;

at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is present;

R_1 , R_4 and R_5 are the same or different and are selected from the group consisting of hydrogen, a ~~cyclic aliphatic~~ alicyclic group, a ~~cyclic heteroaliphatic~~ heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a

alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group and a substituted alkylheteroaryl group;

R₂ and R₃ are the same or different and are selected from the group consisting of hydrogen, a cyclic aliphatic an alicyclic group, a cyclic heteroaliphaticheterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and p-*aro*yl-glutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or

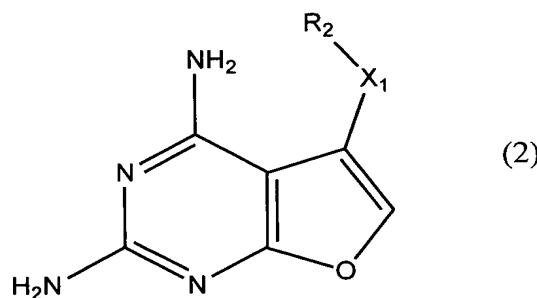
alkynl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

Page 9, last paragraph which wraps to page 10:

Also included within the scope of the present invention are cyclic aliphatic (or “alicyclic”) groups, as that term is understood in the art, and heterocyclic groups. As used herein, the term “heterocyclic group” will refer to non-aromatic cyclic substituents in which one or more members of the ring is not carbon, for example oxygen, sulfur or nitrogen.

Page 11, line 20, wrapping through to page 13, line 14

In preferred embodiments, compounds of the present invention will have the general formula (2):



R₆

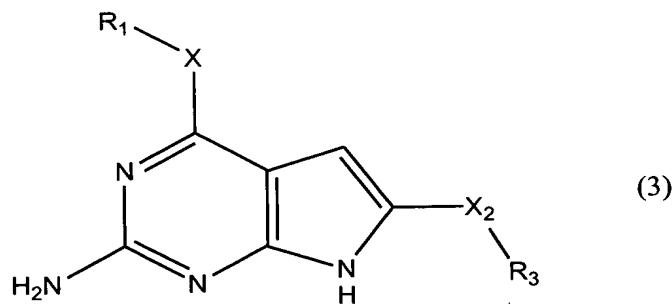
where X₁ is CH=C, and R₆ is selected from the group consisting of hydrogen and a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

R₂ is selected from the group consisting of hydrogen, a cyclic aliphatic an alicyclic group, a cyclic heteroaliphaticheterocyclic group, an aryl group, a heteroaryl group,

an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and *p*-aroylglutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or alkynyl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

In additional preferred embodiments, compounds of the present invention will be represented as having the general formula (3):



where X and X₂ are from one to about three atoms, are the same or different and are independently selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, a heteroalkyl group and a heteroalkenyl group,

and any carbons or nitrogens of said alkyl group, alkenyl group, heteroalkyl group or heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

at least one of R₁ or R₃ are present;

R₁ is selected from the group consisting of hydrogen, a ~~cyclic aliphatic and alicyclic~~ group, a ~~cyclic heteroaliphatic group, a cyclic aromatic group, a heterocyclic aromatic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group and a substituted alkylheteroaryl group;~~

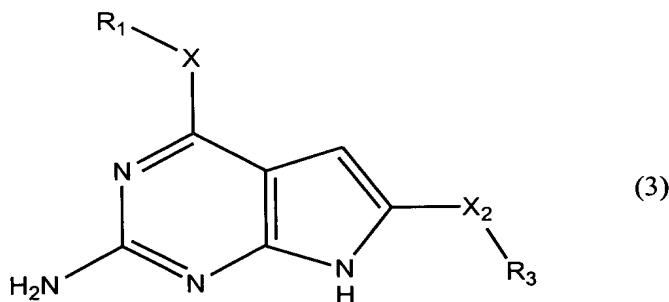
R₃ is selected from the group consisting of hydrogen, a ~~cyclic aliphatic and alicyclic~~ group, a ~~cyclic heteroaliphatic heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group~~

group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and *p*-aroyl-glutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or alkynyl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

In the claims:

22. (Amended) A compound, and pharmaceutically acceptable salts, solvates and prodrugs thereof, having the formula (3):



where X and X₂ are from one to about three atoms, are the same or different and if R₁ or R₃ is not present, are independently selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, an heteroalkyl group and an heteroalkenyl group, and if R₁ or R₃ is present, X and X₂ are independently selected from the group consisting of an alkylene group, a heteroalkylene group, an alkenylene group and a heteroalkenylene group;

and any carbons or nitrogens of said alkyl group, alkylene group, alkenyl group, alkenylene group, heteroalkyl group, heteroalkylene group, heteroalkenylene group or

heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

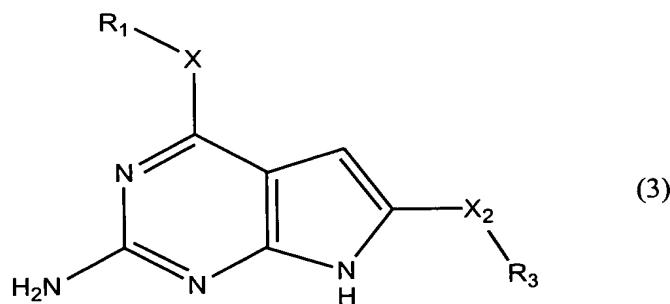
at least one of R₁ or R₃ is present;

if present, R₁ is selected from the group consisting of hydrogen, a cyclic aliphatic group, a cyclic heteroaliphatic group, a cyclic aromatic group, a heterocyclic aromatic group, an alicyclic group, a heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group and a substituted alkylheteroaryl group;

if present, R₃ is selected from the group consisting of hydrogen, a cyclic aliphatic group, a cyclic heteroaliphatic group, an alicyclic group, a heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and p-arooyl-glutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or alkynl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

29. (Amended) A method of treating a patient with an illness by inhibiting at least one enzyme selected from the group consisting of a receptor tyrosine kinase, dihydrofolate reductase and thymidylate synthase, for treatment of a disease condition in a patient, mediated by inhibition of any of these enzymes, by administering to a patient in need thereof an effective amount of a compound having the formula (3):



where X and X₂ are from one to about three atoms, are the same or different and if R₁ or R₃ is not present, are independently selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, an heteroalkyl group and an heteroalkenyl group, and if R₁ or R₃ is present, X and X₂ are independently selected from the group consisting of an alkylene group, a heteroalkylene group, an alkenylene group and a heteroalkenylene group;

and any carbons or nitrogens of said alkyl group, alkylene group, alkenyl group, alkenylene group, heteroalkyl group, heteroalkylene group, heteroalkenylene group or heteroalkenyl group can optionally be substituted with a straight, branched or cyclic lower alkyl group of from 1 to about 6 carbons;

at least one of R₁ or R₃ is present;

if present, R₁ is selected from the group consisting of hydrogen, a cyclic aliphatic group, a cyclic heteroaliphatic group, a cyclic aromatic group, a heterocyclic aromatic group, an alicyclic group, a heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group and a substituted alkylheteroaryl group;

if present, R₃ is selected from the group consisting of hydrogen, a cyclic aliphatic group, a cyclic heteroaliphatic group, an alicyclic group, a heterocyclic group, an aryl group, a heteroaryl group, an alkylaryl group, a alkylheteroaryl group, a substituted aryl group, a substituted heteroaryl group, a substituted alkylaryl group, a substituted alkylheteroaryl group, and *p*-acetyl-glutamate;

and each substituent of any substituted group is the same or different and is selected from the group consisting of a straight, branched or cyclic lower alkyl, alkenyl or alkynyl group of from one to about 6 carbons, an alkoxy group, an alkoxyaryloxy group, and a halogen.

31. The method of Claim 29, wherein said illness disease condition is cancer tumor growth, cell proliferation or angiogenesis.

32. The method of Claim 29, wherein said illness disease condition is selected from the group consisting of infection caused by *Pneumocystis carinii*, *Toxoplasma gondii*, *Mycobacterium tuberculosis* and *Mycobacterium avium*.

34. The method of Claim 30, including further comprising the step of administering said compound by a method selected from the group consisting of parenteral administration, oral administration and topical administration.

Please add the following new claims:

35. The compound of Claim 22, wherein X is NH-.

36. The compound of Claim 35, wherein R₁ is *m*-bromobenzene.

37. The compound of Claim 36, wherein X₂ is CH₂-CH₂.

38. The compound of Claim 37, wherein R₃ is 2-pyridine.

39. The compound of Claim 37, wherein R₃ is benzene.

40. The compound of Claim 37, wherein R₃ is *p*-methoxy benzene.

41. The compound of Claim 37, wherein R₃ is *o*-chlorobenzene.

42. The compound of Claim 37, wherein R₃ is 1-naphthalene.

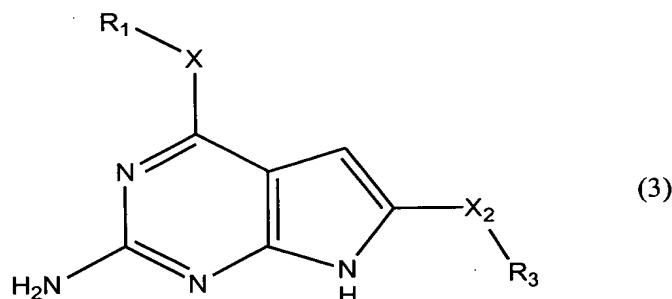
43. The compound of Claim 37, wherein R₃ is 2-naphthalene.

44. The compound of Claim 29, wherein X is NH-.

45. The compound of Claim 44, wherein R₁ is *m*-bromobenzene.
46. The compound of Claim 45, wherein X₂ is CH₂-CH₂.
47. The compound of Claim 45, wherein R₃ is 2-pyridine.
48. The compound of Claim 45, wherein R₃ is benzene.
49. The compound of Claim 45, wherein R₃ is *p*-methoxy benzene.
50. The compound of Claim 45, wherein R₃ is *o*-chlorobenzene.
51. The compound of Claim 45, wherein R₃ is 1-naphthalene.
52. The compound of Claim 45, wherein R₃ is 2-naphthalene.

In the abstract:

This invention discloses pyrrolo pyrimidine compounds, and pharmaceutically acceptable salts, solvates and prodrugs thereof, of the following formula (3): useful in therapeutically and/or prophylactically treating patients with cancer by inhibiting receptor tyrosine kinases and/or dihydrofolate reductase and/or thymidylate synthase. The compounds, and methods of using these compounds, are disclosed.



These compounds are useful in therapeutically and/or prophylactically treating patients with cancer by inhibiting receptor tyrosine kinases and/or dihydrofolate reductase and/or thymidylate synthase. Methods of using these compounds are also disclosed.

TABLE 1

EGFR Kinase Inhibition

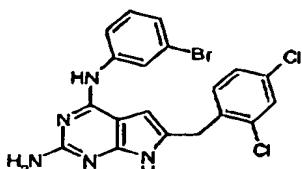
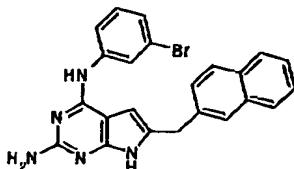
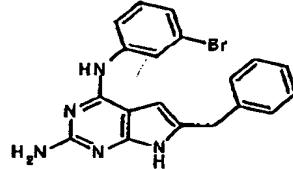
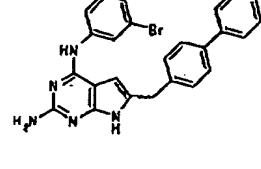
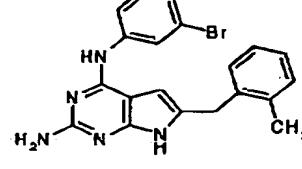
Sample Number	Structure	$IC_{50}(\mu M)$
YJ/AG 176		0.2
YJ/AG 146		1.2
YJ/AG 156		1.7
YJ/AG 145		4.3
YJ/AG 154		6.2
YJ/AG 168		9.2

TABLE 1

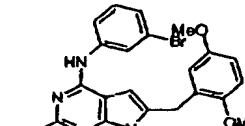
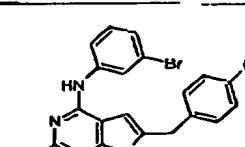
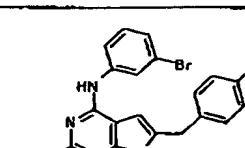
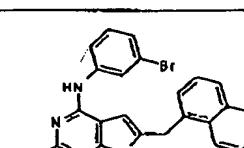
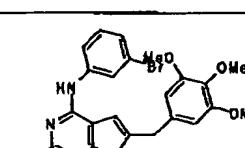
YJ/AG 178		12.6
YJ/AG 140		17.4
YJ/AG 148		19.8
YJ/AG 158		>50
YJ/AG 177		>50
PD153035		0.2
SU5416		ND

TABLE 2

FIK1 Kinase Inhibition

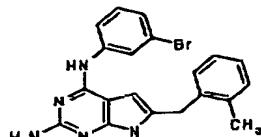
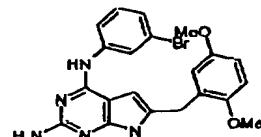
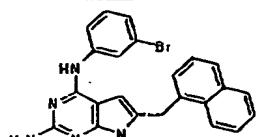
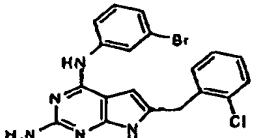
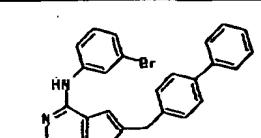
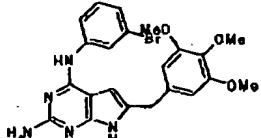
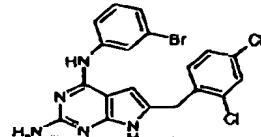
Sample Number	Structure	$IC_{50}(\mu M)$
YJ/AG 168		0.3
YJ/AG 178		0.6
YJ/AG 158		5.1
YJ/AG 145		5.6
YJ/AG 154		6
YJ/AG 177		9.4
YJ/AG 176		28.1

TABLE 2

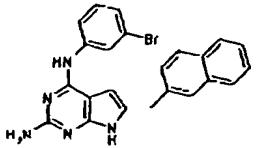
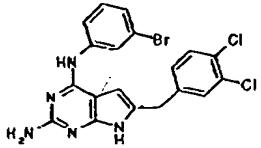
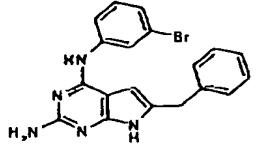
YJ/AG 140		ND
YJ/AG 146		>50
YJ/AG 148		>50
YJ/AG 156		>50
PD153035		ND
SU5416		2.4

TABLE 3

A431 Cytotoxicity

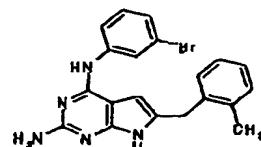
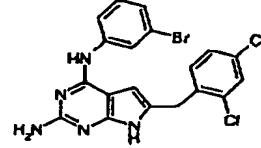
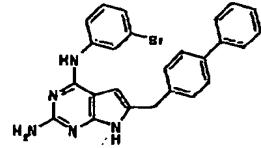
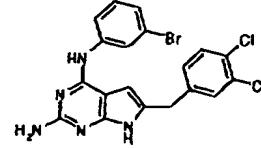
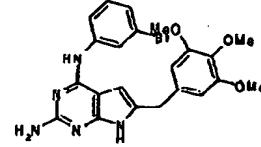
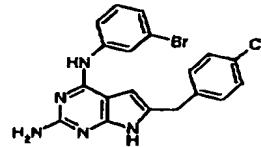
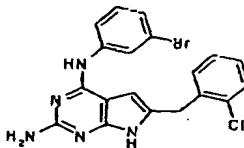
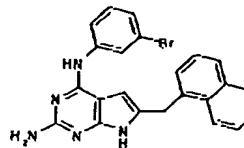
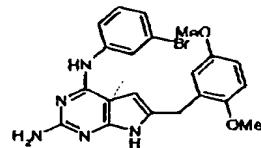
Sample Number	Structure	$IC_{50}(\mu M)$
YJ/AG 168		1.2
YJ/AG 176		2.8
YJ/AG 154		23.5
YJ/AG 146		33.2
YJ/AG 148		33.5
YJ/AG 177		42.1
YJ/AG 140		ND

TABLE 3

YJ/AG 145		>50
YJ/AG 158		>50
YJ/AG 178		>50
YJ/AG 156		>50
PD153035		12.6
SU5416		19.2